Safety of *in vitro* amplified HLA-haploidentical donor immune cell infusions for childhood malignancies

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Abstract   *In vitro* amplified human leukocyte antigen (HLA)–haploidentical donor immune cell infusion (HDICI) is not commonly used in children. Therefore, our study sought to evaluate its safety for treating childhood malignancies. Between September 2011 and September 2012, 12 patients with childhood malignancies underwent HDICI in Sun Yat-sen University Cancer Center. The median patient age was 5.1 years (range, 1.7–8.4 years). Of the 12 patients, 9 had high-risk neuroblastoma (NB) [7 showed complete response (CR), 1 showed partial response (PR), and 1 had progressive disease (PD) after multi-modal therapies], and 3 had Epstein-Barr virus (EBV)–positive lymphoproliferative disease (EBV-LPD). The 12 patients underwent a total of 92 HDICIs at a mean dose of 1.6×10^8 immune cells/kg body weight: 71 infusions with natural killer (NK) cells, 8 with cytokine-induced killer (CIK) cells, and 13 with cascade primed immune cells (CAPRIs); 83 infusions with immune cells from the mothers, whereas 9 with cells from the fathers. Twenty cases (21.7%) of fever, including 6 cases (6.5%) accompanied with chills and 1 (1.1%) with febrile convulsion, occurred during infusions and were alleviated after symptomatic treatments. Five cases (5.4%) of mild emotion changes were reported. No other adverse events occurred during and after the completion of HDIDIs. Neither acute nor chronic graft versus host disease (GVHD) was observed following HDICIs. After a median of 5.0 months (range, 1.0–11.5 months) of follow-up, the 2 NB patients with PR and PD developed PD during HDICIs. Of the other 7 NB patients in CR, 2 relapsed in the sixth month of HDICIs, and 5 maintained CR with disease-free survival (DFS) ranging from 4.5 to 11.5 months (median, 7.2 months). One EBV-LPD patient achieved PR, whereas 2 had stable disease (SD). Our results show that HDICI is a safe immunotherapy for childhood malignancies, thus warranting further studies.

Key words Childhood malignancies, HLA-haploidentical donor cells, immunotherapy, safety

Through modern, standard treatments, 70%–80% of childhood acute lymphoblastic leukemias and malignant lymphomas and 60% of childhood malignant solid tumors could be cured. However, although multi-modal therapies including surgery, chemotherapy, and radiotherapy were used, approximately 30%–40% of childhood

malignant solid tumors eventually relapsed and resulted in patient death. Tumor recurrence is considered to result from minimal residual disease (MRD)[1]. Many studies suggest that tumor immunotherapy with cytokines, vaccines, monoclonal antibodies, and adoptive cell infusions could regulate the patients' immune response, thereby clearing the MRD, reducing tumor recurrence and mortality[2-5].

In recent years, autologous cytokine-induced killer (CIK) cells, tumor infiltrating lymphocytes (TIL), allogeneic CIK cells, and natural killer (NK) cells have been successfully used for adoptive immune cell infusions to cure various adult advanced or metastatic tumors[6-12] through induction of the graft-versus-tumor (GVT) effect. This treatment has previously shown good protection and antitumor effects[11-13] but is less frequently used for child patients with tumors.

Childhood Epstein-Barr virus (EBV)–positive lymphoproliferative disease (EBV-LPD) is a chronic active disease caused by EBV infection. The disease mainly manifests fever, systemic multiple lymphadenectasis, and splenomegaly. A variety of treatment methods, such as anti-viral factors, immune regulatory factors,

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doi: 10.5732/cjc.012.10298

and chemotherapy, have been used to treat EBV-LPD, but the therapeutic efficacy is still poor[14-17]. Adoptive cellular immunotherapy demonstrated positive results in some patients[18-20]. Wang *et al.*[20] have used lymphocytes from the patient's mother to treat childhood EBV-LPD and achieved significant improvements in the clinical outcomes of all 5 patients.

The autologous immune cells of children with malignancy have some functional deficiencies. Furthermore, it is difficult to collect 30–50 mL of peripheral blood from childhood patients to isolate and culture immune cells, such as NK and CIK cells, *in vitro*. Therefore, the application of cellular immunotherapy for these patients is limited. As human leukocyte antigen (HLA)–haploidentical donors, the children's parents are ideal immune cell sources. *In vitro* amplified HLA-haploidentical immune cell infusion (HDICI) is not commonly used in children, especially in Chinese children with malignancy; therefore, further studies are necessary. Our study aimed to evaluate the safety of *in vitro* amplified HLA-HDICI for Chinese children with malignancy.

Patients and Methods

Patient selection

The patient inclusion criteria were as follows: children under the age of 10 years who were pathologically diagnosed with stage IV neuroblastoma and achieved complete remission (CR) or partial remission (PR) after combined modality therapy or children who were pathologically diagnosed with EBV-LPD with rash, fever, and/or swollen lymph nodes; normal heart, liver, brain, renal, and other vital organ functions; no autoimmune diseases; with informed consent signed by the children's legal guardians; the haploidentical donor (father or mother) was healthy with no history of infectious or autoimmune diseases, and the mother should not be pregnant.

The patients who did not meet the above inclusion criteria, who withdrew from therapy, or who should not continue to undergo treatment due to serious adverse events, complications, or special physiologic changes were excluded. The patients who had adverse events were credited in the adverse event analysis.

This study was performed strictly according to the guidelines for human cell therapy and preparation quality control. The cell culture system was also in accordance with the requirements of the guidelines and approved by the Ethics Committee of Sun Yat-sen University Cancer Center. For all children, the informed consent and human cell therapy application were signed by their parents or guardians before cell infusions.

Source, preparation, and infusion of immune cells

The peripheral blood immune cells were adopted from the patient's father or mother. All donors were required to complete routine tests, including blood, biochemical, hemostatic function, hepatitis tests, human immunodeficiency virus (HIV) and Treponema pallidum antibody detection, and electrocardiogram (ECG). All test results should be confirmed as normal, and all donors should sign the informed consent and the human cell therapy application form. Peripheral blood sample (30–50 mL) was collected from the patient's father or mother and immediately sent to the Biological Therapy Center of Sun Yat-sen University Cancer Center. NK, CIK, and cascade primed immune cell (CAPRI) preparations (100–120 mL) with antitumor effects were prepared according to the regulations of *in vitro* culture of human immune cells in our institute.

Routine blood test, liver and renal functions, and conventional ECG were reexamined on the patients before each HDICI. All results should be confirmed as normal before HDICI. A Phenergan (1 mg/kg) intramuscular injection was performed 30 min before HDICI to prevent fever or allergic reactions. To ensure immune cell activity, the infusion should be completed within 1 h. During the first month, HDICIs were performed weekly; in the second month, HDICIs were performed biweekly; since the third month, HDICIs were performed monthly. Under special conditions, the infusion interval could be appropriately adjusted.

Observation of adverse reactions during HDICIs

During each HDICI and within 2 h after infusion, the ECG and blood oxygen saturation monitors were used to monitor the patient's breathing, pulse, blood pressure, and blood oxygen saturation, and body temperature was also monitored. The children's consciousness, chills, fever, rash, facial flushing, nausea, vomiting, abdominal pain, diarrhea, edema, allergic reactions, mood changes, and other adverse reactions were observed and recorded according to the National Acute and Subacute Toxicity Reaction Grading Standards for Anticancer Drugs. The routine blood and biochemical tests were reexamined before each infusion and 1 week after infusion.

Clinical assessments

Version 1.1 of the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) was used for the preliminary clinical assessment of the patients every month. CR is defined as the disappearance of all lesions. PR is defined as a $\geqslant$ 30% decrease of lesion diameter. PD is defined as a $\geqslant$ 20% increase of lesion diameter. SD is defined as lesions with a diameter change between PR and PD.

Results

Patients' characteristics

Twelve patients with childhood malignancy, 6 boys and 6 girls with a median age of 5.1 years (range, 1.7 to 8.4 years), were treated at Sun Yat-sen University Cancer Center between September 2011 and September 2012.

Nine patients had stage IV high-risk neuroblastoma. After comprehensive treatment including surgery, chemotherapy, and radiotherapy, 7 patients achieved CR, 1 achieved PR, and 1 had PD (Table 1). The PD patient's parents requested adoptive immune cell therapy.

Three patients had EBV-LPD: 2 had T-cell disease and 1 had

B-cell disease (**Table 2**).

Detailed information of HDICIs

Ten patients were treated with simple maternal immune cell infusions, whereas 2 were treated with paternal and maternal immune cell infusions (**Table 3**). A total of 92 HDICIs were performed on the 12 patients. Each infusion was scheduled over 2 days such that half the amount of cells was used for each daily infusion. Four infusions were considered as a course. The required endotoxin and sterility detection tests for all amplified immune cells before infusion were negative.

The 9 patients with high-risk neuroblastoma underwent oral isotretinoin and subcutaneous interferon injection while undergoing HDICIs.

Adverse reactions during HDICIs

Of the 92 HDICIs given to the 12 patients, a total of 20 febrile reactions occurred, usually at 2 h after the first infusion on the first day with a 21.7% occurrence rate (**Table 4**). The febrile reactions were accompanied by a slight tachypnea, rapid heart rate, and different degrees of facial flushing, among which 6 reactions displayed chills and rigor. One 2-year-old child displayed fever, apparent chills, and shivers 1.5 h after the tenth HDICI. After 30 min, this child displayed typical febrile convulsion symptoms such as limb stiffness, bilateral eye valgus, apnea, purple facial coloration, and foaming at the mouth associated with a loss of consciousness. Transitory apnea resulted in decreased blood oxygen saturation, but the blood pressure and pulse were stable. After immediate oxygen absorbance, intramuscular administration of phenobarbital sodium (100 mg), and intravenous injection of dexamethasone (2 mg), the above symptoms persisted for approximately 3 min and then gradually subsided. For remaining febrile reactions, the temperature returned to normal within a short time (2 h on average) through physical cooling alone or combined with antifebrile drugs. Dexamethasone (0.1 mg/kg) pretreatment 30 min before HDICI on the second day prevented fever and other adverse reactions during and after the HDICI process in all patients. Two patients displayed slight mood changes during 5 HDICIs, averaging 1 h in duration. No special treatments were performed except for close observation. The children fell asleep 2 h after infusion and felt normal after awakening. The rest of the children maintained normal vital signs during HDICIs. None of the children displayed any nausea, vomiting, abdominal

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Table 1. Clinical characteristics of 9 NB patients before immunotherapy

ID	Gender	Age (years)	N-MYC gene	Status
1	M	4.9	Negative	CR
2	F	1.7	Negative	CR
3	M	8.4	Negative	CR
4	M	4.7	Negative	CR
5	F	5.3	Negative	PD
6	F	6.6	Negative	CR
7	F	2.6	Negative	CR
8	M	2.6	Negative	CR
9	F	4.7	Positive	PR

NB, neuroblastoma; M, male; F, female; CR, complete response; PR, partial response; PD, progressive disease. All patients had stage IV disease according to the International Neuroblastoma Staging System (INSS).

Table 2. Clinical characteristics of 3 EBV-LPD patients before immunotherapy

ID	Gender	Age (years)	Symptoms and signs	Classification	Initial EBV DNA copies
10	M	8.1	Low-grade fever, rashes on both hands and feet, multiple divergence in yellow hydroa vacciniforme with itching	Hydroa vacciniforme skin-like T-cell lymphoma	1.2×10^8
11	F	4.7	Bilateral cervical, axillary, inguinal lymphadenopathy, no fever, night sweat	EBV-related T-cell LPD	1.9×10^5
12	M	6.3	Right side lower jaw lymphadenopathy, no fever, night sweat	Chronic active EBV-infected B-cell LPD	2.5×10^4

EBV, Epstein-Barr virus; EBV-LPD, EBV-positive lymphoproliferative disease.

Table 3. Detailed information of HDICIs in 12 patients

ID	Weight (kg)	Number of infusions				Average amount ($\times 10^8$ cells/kg)
		NKs	CIKs	CAPRIs	Total	
1	17.0	8	0	0	8	1.4
2	12.0	11	0	0	11	2.1
3	30.0	8	0	0	8	1.0
4	15.0	10	0	0	10	1.7
5	18.0	4	4	0	8	2.5
6	20.0	5	0	0	5	1.8
7	12.5	7	0	0	7	1.9
8	20.0	10	0	0	10	1.2
9	23.5	8	4	0	12	1.8
10	30.0	0	0	3	3	1.0
11	25.0	0	0	4	4	1.1
12	20.0	0	0	6	6	1.1
Total	–	71	8	13	92	1.6

HDICI, human leukocyte antigen (HLA)–haploidentical donor immune cell infusion; NKs, natural killer cells; CIKs, cytokine-induced killer cells; CAPRIs, cascade primed immune cells. Patient No. 2 underwent 5 infusions with NKs from the father, then 6 infusions with NKs from the mother. Patient No. 5 underwent 4 infusions with CIKs from the mother, then 4 infusions with NKs from the father. Patient No. 9 underwent 8 infusions with NKs from the mother, then 4 infusions with CIKs from the mother. All other patients underwent infusions with NKs from the mother.

Table 4. Adverse reactions during and after HDICIs in 12 patients

ID	Adverse reactions (cases)			
	Fever	Convulsion	Flush	Mood changes
1	0	0	0	2
2	5	1	5	0
3	0	0	0	0
4	2	0	2	0
5	4	0	4	0
6	0	0	0	0
7	2	0	2	0
8	2	0	2	0
9	4	0	4	0
10	1	0	1	0
11	0	0	0	0
12	0	0	0	3
Total	20	1	20	5

pain, diarrhea, rash, swelling, allergic reactions, or other adverse reactions. Furthermore, no obvious abnormality in hemogram, serum electrolytes, hepatic and renal functions, blood lipid levels, or C-reaction protein (CRP) was observed.

During the observation period and follow-up, no acute or chronic graft versus host disease (GVHD) was observed.

Preliminary efficacy evaluation

The patients were followed up for 1.0 to 11.5 months, with a median of 5.0 months. One neuroblastoma patient with PR and 1 with PD showed tumor progression. Of the 7 patients with CR, 2 displayed recurrence 6 months after the first HDICI, and 5 sustained CR with disease-free survival (DFS) ranging from 4.5 to 11.5 months

(median, 7.2 months). Of the 3 BV-LPD patients, 1 achieved PR, and 2 displayed SD.

Discussion

In the present study, 12 children with malignancy underwent a total of 92 HDICIs. All HDICIs were safe. No acute or chronic GVHD was found during HDICIs and follow-up, which was similar with other studies. Rooney et al.[21] have used allogeneic cytotoxic ($CD4^+CD8^+$) T-cell infusions to prevent and treat EBV-induced lymphomas in 39 children who underwent allogeneic bone marrow transplantations. No patients showed obvious abnormalities in liver or renal functions or on the chest radiograph during the infusion process. No acute GVHD was found in the 39 patients, although 1 demonstrated chronic GVHD prior to cell infusion. During the 15- to 54-month (median, 30-month) follow-up, 27 patients survived, 9 died of tumor recurrence, 2 died of infection, and 1 died of pneumonia. Kloess et al.[22] have used interleukin-2 (IL-2)–activated NK cell infusions to treat 4 children with stage IV neuroblastoma who did not respond to allogeneic hematopoietic stem cell transplantations or standard treatments. The infusion process was safe, and no fever, allergic reactions, GVHD, or other adverse events were found.

GVHD is mainly related to the compatibility of the recipient's and donor's HLA molecules and the amount of the donor's immune cells. NK cells can non-specifically and directly kill target cells. This natural killer activity does not require prior antigen sensitization or antibody participation and has no restriction on major histocompatibility complex (MHC). Therefore, using amplified HLA-haploidentical NK cell infusion has a low risk of GVHD. Lisbeth et al.[13] have performed *in vitro* amplified allogeneic NK and NK-like T-cell infusions for 5 patients who underwent allogeneic hematopoietic stem cell transplantations. The process of cell infusion alone or in combination with subcutaneous injection of IL-2 was safe. Additionally, there were no acute GVHD symptoms or other adverse reactions. Six months after cell infusion, 2 patients were still alive, whereas 3 died of tumor progression. The impaired alloreactivity of T cells during the cell culture process was considered to reduce the risk of GVHD. The alloreactivity of T cells significantly decreased or even disappeared when the cells were cultured for more than 7 days. However, the exact mechanism is still unclear. The HDICI donors' CIK and CAPRI cells contain a large number of T lymphocytes, which may induce GVHD in theory but is relatively safe during clinical applications. Verneris et al.[23] proposed that because the donor CIK and CAPRI cells have special biological characteristics compared with other lymphocytes, they can overcome the obstacles of HLA molecules, reduce the alloreactivity, and thus significantly reduce the risk of GVHD. Baker et al.[24] have demonstrated that the donor CIK cells could secrete large amounts of interferon-γ (IFN-γ), a cytokine known to strongly suppress GVHD. Therefore, donor CIK cell infusion causes a very low risk of GVHD, which has been confirmed in many pre-clinical trials.

The occurrence of GVHD is related to not only the HLA compatibility but also the number of donor immune cells. Luznik et al.[25] have reported that when the amount of donor immune cells was less than 1×10^7 cells/kg, they usually would neither induce GVHD nor have the GVT effect. When the amount of donor immune cells was more than or equal to 1×10^7 cells/kg, the GVT effect was significant, but the incidence of acute GVHD was approximately 0–30%. When the amount of donor immune cells was more than or equal to 1×10^8 cells/kg, the GVT effect was significant, and the incidence of acute GVHD was approximately more than 50%. In the present study, the average amount of donor immune cells for the 92 infusions was 1.6×10^8 cells/kg (range, 1.0×10^8 to 3.4×10^8 cells/kg). During the infusion, no GVHD was observed. Wang et al.[20] have used maternal lymphocyte infusions to treat 5 patients with transplantation-unrelated, EBV-positive T-cell LPD. No significant GVHD was observed. Tokita et al.[26] considered that alloreactive T cells exist in maternal lymphocytes, which can induce GVHD. However, infant-maternal microchimerism exists in the blood of children with malignancy, suggesting that immune tolerance exists between the maternal generation and their offspring. Therefore, the maternal lymphocyte infusion could be used to treat patients with T-cell EBV-LPD.

In the present study, after HLA-haploidentical NK, CIK, and CAPRI cells were amplified for 2 weeks (more than 7 days) *in vitro*, the amount of alloreactive T cells was significantly reduced, and the alloreactivity was partly or completely lost. In addition, no acute or chronic GVHD was found during the infusion and follow-up due to the presence of infant-maternal microchimerism.

In brief, HDICI immunotherapy is safe for treating childhood malignancies, without causing GVHD. The main adverse reactions include fever, facial flushing, and mild mood changes. However, due to the small number of patients in this study, the efficacy of HDICI needs to be further examined using a larger sample size.

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